Journal of Physiology (1989), **411**, *pp.* 367–377
With 2 text-figures
Printed in Great Britain

THE VENTILATORY CO_2 SENSITIVITIES FROM READ'S REBREATHING METHOD AND THE STEADY-STATE METHOD ARE NOT EQUAL IN MAN

BY A. BERKENBOSCH, J. G. BOVILL, A. DAHAN, J. DEGOEDE AND I. C. W. OLIEVIER

From the Departments of Physiology and Anaesthesiology, University of Leiden, P.O. Box 9604, 2300 RC Leiden, The Netherlands

(*Received 15 July 1988*)

SUMMARY

1. The ventilatory response to changes in end-tidal carbon dioxide tension during hyperoxia, obtained with Read's rebreathing method and a steady-state technique, were compared.

2. In ten young male subjects, forty successful rebreathing and thirteen steady-state experiments were performed on thirteen different morning sessions.

3. In all subjects the ventilatory CO_2 sensitivities obtained with the rebreathing method (S_r) were appreciably larger than the steady-state CO_2 sensitivities (S_s). The ratio S_r/S_s ranged from 1·40 to 2·59 with a mean value of 1·85.

4. We argue that these results can be explained by considering the effect of changes in cerebral blood flow upon increasing the arterial CO_2 tension during rebreathing and the steady state.

5. We conclude that in general the CO_2 sensitivity obtained with Read's rebreathing method does not represent the steady-state CO_2 sensitivity.

INTRODUCTION

In 1967 Read introduced a rebreathing technique to obtain the ventilatory response to carbon dioxide. Since then, this technique has been extensively used in clinical and fundamental research. In contrast to earlier rebreathing techniques, which yielded non-linearities in the ventilatory carbon dioxide response curves (Landmesser, Cobb, Peck & Converse, 1957), Read used a small rebreathing bag of 4–6 l filled with a gas mixture of 7% CO_2 in oxygen. Under these conditions rebreathing was initiated at a CO_2 tension close to that of mixed venous blood (P_{v,CO_2}) and a rapid equilibrium was established between the CO_2 tension in mixed venous blood, arterial blood and gas in the lung and rebreathing bag. It was then found experimentally that the subsequent increase of end-tidal CO_2 tension (P_{ET,CO_2}) and ventilation ($\dot{V}_E$) were linear in time. The results obtained with this type of rebreathing method (which will be referred to as Read's method) are generally interpreted as follows. Initiating the rebreathing close to the mixed venous CO_2 tensions leads to a greatly reduced arterial–tissue CO_2 gradient and the rapid establishment of equality

between P_{ET,CO_2}, arterial P_{CO_2} (P_{a,CO_2}), P_{v,CO_2} and presumably brain tissue P_{CO_2} (P_{t,CO_2}), all increasing with the same rate of rise (Rebuck & Slutsky, 1981).

In experiments performed on three subjects, Read (1967) compared his rebreathing technique with the steady-state method. He found good agreement between the ventilatory CO_2 sensitivities measured with both methods. However, there is ample evidence that an increase in P_{a,CO_2} results in an increased cerebral blood flow, which is reflected in a decreased arterial–cerebral venous CO_2 gradient in the steady state (Kety & Schmidt, 1948; Lambertsen, Hall, Wollman & Goodman, 1963; Fencl, Vale & Broch, 1969; Nishimura, Suzuki, Nishiura, Yamamoto, Miyamoto, Kishi & Kwakami, 1987). Therefore, the slope of the $\dot{V}_E$–P_{t,CO_2} curve must be steeper than that of the steady-state $\dot{V}_E$–P_{a,CO_2} curve. In a theoretical analysis, Read & Leigh (1967) showed that initiating rebreathing at the mixed venous level leads to a nearly equal change in time of P_{a,CO_2} and P_{t,CO_2}, with a slope close to unity. They pointed out that the slope of the rebreathing response was about 20–30% steeper compared to that of the steady-state curve. They suggested that the reason why this difference in slopes was not detected in the experiments of Read (1967) was because of the relatively small P_{ET,CO_2} range covered in the steady-state experiments and the variability of repeated experiments.

To the best of our knowledge no systematic study has been published validating Read's rebreathing method against the steady-state method. We have therefore performed such a study in a group of subjects on whom repeated rebreathing experiments were performed.

METHODS

Subjects

Ten healthy male subjects, aged 21–27 years, who gave their informed consent, took part in the experimental protocol approved by the Leiden University Ethics Committee. The subjects were naive to respiratory physiology with the exception of subject A.D.A. None of the subjects was a smoker or had any history of chronic obstructive pulmonary disease. Each subject was familiarized with the experimental procedure on the day before testing. All subjects refrained from stimulant and depressant substances 12 h prior to the experiment.

Measurements and procedures

An oronasal face mask was fitted and the subjects were instructed to breathe through their mouths to prevent a change in airway resistance during the experiment. The airway gas flow was measured with a Fleisch No. 3 pneumotachograph connected to a differential pressure transducer (Hewlett–Packard Model 270, USA) and electronically integrated (Drummond & Goodenough, 1977) to yield a volume signal. The CO_2 concentrations of the inspired and expired gases were measured with a fast-response infra-red analyser (Gould Godart Mk 2 capnograph, The Netherlands) and the O_2 concentrations with a fast-response zirconium oxide cell (Jaeger O_2 test, FRG). All signals were recorded on a polygraph, and also digitized and processed by a PDP 11/23 computer. The tidal volume, inspiratory time, expiratory time, respiratory frequency, $\dot{V}_E$ (expiratory ventilation), end-tidal CO_2 and end-tidal O_2 tensions were stored on a breath-to-breath basis. In this study we will generally assume that end-tidal P_{CO_2} is equal to arterial P_{CO_2}.

In the steady-state experiments the pneumotachograph was connected to a T-piece. One arm of the T-piece received a gas mixture with a flow of 40 l min^{-1} from a gas mixture system, consisting of three mass flow controllers (Bronkhorst High Tech BV-F202, The Netherlands) by which the flow of O_2, N_2 and CO_2 could be set individually at a desired level. The computer provided control signals to the mass flow controllers, so that the composition of the inspiratory gas mixture could be adjusted to force the P_{ET,CO_2} to follow a specific dynamic pattern in time and keep the end-tidal P_{O_2} (P_{ET,O_2}) constant. In the rebreathing experiments the subjects started by breathing a hyperoxic

gas mixture. Subsequently they were connected to a balloon filled with 6 l of a gas mixture consisting of 7 % CO_2 and 75–80 % O_2 in N_2 by turning a three-way valve. The instrumental dead space was 280 ml.

Experimental design

After arrival at the laboratory the subjects rested for 30 min on a comfortable chair. Subsequently the face mask was fitted and the experiments started. They were encouraged to read or listen to music through headphones. The experiments, performed on the same morning, started with steady-state experiments, followed by rebreathing experiments. Each session lasted approximately 3·5 h. To obtain data points for the steady-state ventilatory response, four to five stepwise P_{ET,CO_2} elevations were applied. The steps varied from 1 to 2·5 kPa. The order of the steps was randomly determined. Each steady-state experiment started with a period of steady-state ventilation of approximately 5 min during which the P_{ET,CO_2} was held slightly above resting P_{ET,CO_2} (varying among subjects from 5·4 to 5·8 kPa). The P_{ET,CO_2} was then elevated within one or two breaths, maintained constant for 8 min and then returned to the original value for a further 8 min. During all experiments the P_{ET,O_2} was held constant at a hyperoxic level of 70 kPa. In the rebreathing experiments subjects initially inspired a gas mixture with an F_{I,O_2} (inspiratory fractional concentration of oxygen) > 0·8 for 5 min. After a maximum expiration the subject was connected to the balloon by turning a valve. Rebreathing was continued for at least 3 min. The subjects rested for 15 min between individual runs. At least three rebreathing response curves were obtained per session.

To obtain information on the reproducibility of the response curves the experiments were repeated 2 weeks later in three subjects.

Data analysis

In the steady-state experiments the $\dot{V}_E$ and P_{ET,CO_2} were averaged over ten breaths. Data points were collected in the minute before the CO_2 increase, in the minute before the CO_2 decrease and in the last minute of the experiment. In the rebreathing experiments breath-to-breath data points were used. Data obtained from the first 30 s after the start of rebreathing were excluded from the data analysis, as were sighs and swallows. The CO_2 sensitivities for steady-state and rebreathing methods were calculated by linear regression of $\dot{V}_E$ on P_{ET,CO_2}. For rebreathing experiments the rate of rise of the P_{ET,CO_2} was calculated for each run from linear regression of P_{ET,CO_2} on time. The difference between the P_{ET,CO_2} just after the step and the resting P_{ET,CO_2}, measured during the minute preceding the start of rebreathing, was taken as an estimate of the step increase in P_{ET,CO_2} at the start of rebreathing.

RESULTS

A total of thirteen steady-state responses and forty-three rebreathing responses were obtained on thirteen different morning sessions. Due to technical problems three rebreathing curves had to be discarded. All subjects completed the three minutes of rebreathing without discomfort. In Fig. 1 a typical recording of a rebreathing experiment is shown. After steady-state ventilation the subject expired to residual volume and was then connected to the rebreathing bag. Due to the CO_2 in the bag the P_{ET,CO_2} increased rapidly to 7·0 kPa, whereafter the P_{ET,CO_2} increased with a rate of rise of 0·45 kPa min^{-1}. Note that after the second breath following the step increase in P_{ET,CO_2}, inspiration and expiration P_{CO_2} levels become equal, indicating an equilibrium between mixed venous blood and gas in the lung and rebreathing bag. After omitting the first 30 s of the response all rebreathing curves showed a linear increase of breath-to-breath ventilation with time. None of the steady-state response curves showed evident non-linearities as judged by the naked eye and all were accepted. The results of the experiments are summarized in Table 1.

In all subjects the CO_2 sensitivity derived from the rebreathing experiments (S_r)

was greater than that derived from the steady-state experiments (S_s). The mean ratio S_r/S_s was 1·85, ranging from 1·40 to 2·59. In Fig. 2 a rebreathing response together with the steady-state response of subject E.V.D. is plotted. The fitted lines converge at high P_{ET,CO_2} levels, illustrating the increased slope of the response during rebreathing. The mean peak ventilation obtained in the steady-state experiments was 35 l min^{-1} and 45 l min^{-1} in the rebreathing experiments.

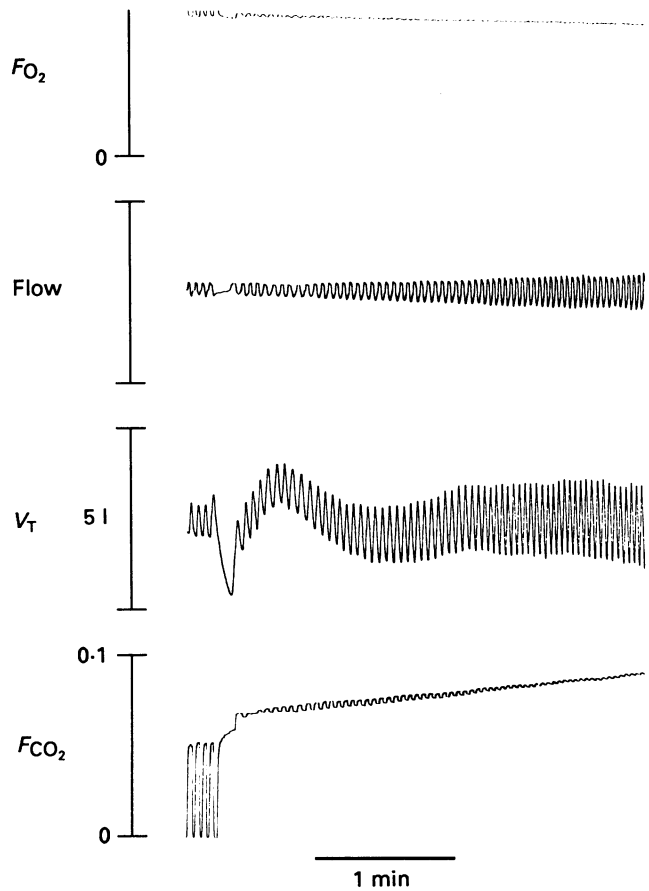

Fig. 1. Oscillographic recording of a rebreathing experiment of subject E.V.W. The flow signal is not calibrated. F_{O_2} and F_{CO_2}, fractional concentration of O_2 and CO_2, respectively. V_T, tidal volume.

The within-day variability of S_r ranged from 2% in subject R.R.A to 34% in subject E.V.W. with a coefficient of variation for the whole group of roughly 15%. On the second session the within-day variability (10–20%) was somewhat higher for all three subjects. Two subjects had an almost identical mean response in the first and second session whereas the rebreathing slope of subject E.V.D. almost doubled in the second session. The steady-state response in the first and second session showed good correspondence.

TABLE 1. Values of the parameters S_r (rebreathing slope), A (step increase in P_{ET,CO_2}), R (rate of rise of P_{ET,CO_2} in time) and S_s (steady-state slope). n is the number of rebreathing experiments

Subject	n	S_r (l min^{-1} kPa^{-1})	A (kPa)	R (kPa min^{-1})	S_s (l min^{-1} kPa^{-1})
		First session			
A.D.A.	4	18·7 ± 1·9	1·2 ± 0·1	0·80 ± 0·52	10·6 ± 0·7
E.V.D.	3	10·8 ± 1·4	1·4 ± 0·1	0·41 ± 0·05	7·5 ± 0·4
E.V.W.	2	15·2 ± 5·1	1·6 ± 0·1	0·56 ± 0·17	10·9 ± 0·9
M.T.O.	3	21·7 ± 2·2	1·2 ± 0·1	1·41 ± 0·03	12·7 ± 1·8
P.V.E.	3	15·8 ± 1·3	1·9 ± 0·1	0·47 ± 0·10	7·4 ± 0·4
G.L.Y.	3	24·6 ± 5·4	1·7 ± 0·1	0·34 ± 0·05	9·5 ± 0·9
M.G.I.	3	19·5 ± 3·6	1·7 ± 0·1	0·53 ± 0·01	10·1 ± 1·2
E.V.H.	3	16·9 ± 5·0	1·3 ± 0·1	0·56 ± 0·13	9·0 ± 0·7
J.J.A.	3	14·1 ± 0·4	1·6 ± 0·1	0·56 ± 0·04	8·2 ± 0·7
R.R.A.	2	10·6 ± 0·2	1·4 ± 0·1	0·64 ± 0·05	5·1 ± 0·5
Mean		16·8 ± 4·5	1·5 ± 0·2	0·53 ± 0·13	9·1 ± 2·2
		Second session			
E.V.D.	6	20·3 ± 4·0	1·3 ± 0·1	0·28 ± 0·06	9·6 ± 1·0
P.V.E.	3	15·3 ± 1·7	1·6 ± 0·04	0·59 ± 0·07	7·0 ± 0·6
R.R.A.	2	9·9 ± 1·0	1·4 ± 0·03	0·56 ± 0·04	5·8 ± 0·8
Mean		15·2 ± 5·2	1·4 ± 0·1	0·48 ± 0·17	7·5 ± 1·9

The values are mean ± standard deviation.

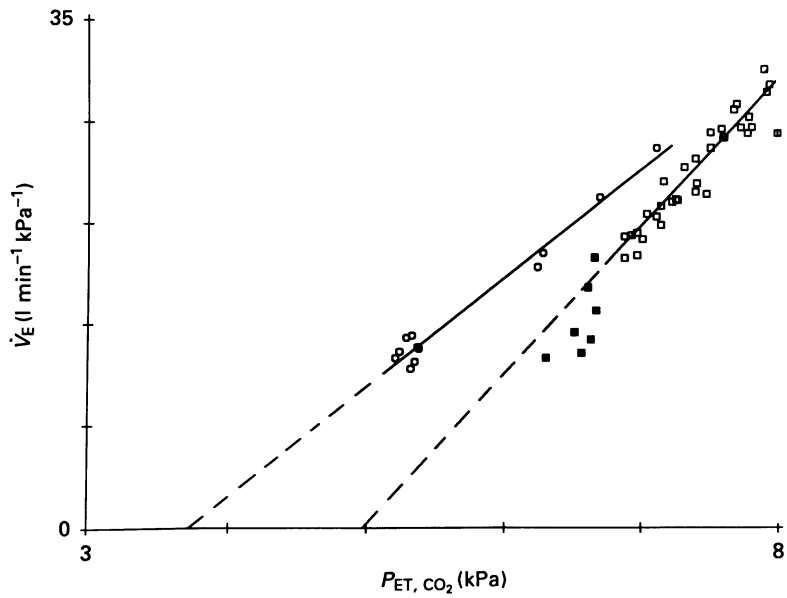

Fig. 2. Ventilatory response of subject E.V.D. obtained with the steady-state method (○) and from one run with the rebreathing method (□). Filled squares denote data points of the first 30 s of the rebreathing experiment and are not used in the linear regression analysis. The steady-state slope is 7·5 l min^{-1} kPa^{-1} and the rebreathing slope is 10·3 l min^{-1} kPa^{-1}.

DISCUSSION

Read (1967) reported in his classic paper that his rebreathing method for determining the ventilatory response to carbon dioxide gave values for the CO_2 sensitivities that were in good agreement with those obtained from the steady-state method. There have been few studies published comparing both methods since Read's original experimental work. Clark (1968) and Linton, Poole-Wilson, Davies & Cameron (1973) reported results which were in agreement with the results of Read (1967). The three subjects studied by Clark (1968) all had chronic airways obstruction and had been chosen for their low responsiveness to carbon dioxide. Linton *et al.* (1973) made a comparison in six subjects, but presented only mean values for the whole group. On the other hand, Honda & Miyamura (1972) and Jacobi, Patil & Saunders (1987) found that the rebreathing technique overestimated the steady-state CO_2 sensitivity. Honda & Miyamura (1972) compared the slope of the rebreathing response and the steady-state response in two subjects on six subsequent days. The slopes of the rebreathing response curves progressively increased until the third day and then levelled off. They found a mean ratio S_r/S_s of 1·5. Jacobi *et al.* (1987) studied nine subjects and found a mean ratio S_r/S_s of 2·3. We performed forty rebreathing experiments and thirteen steady-state experiments in ten subjects. In all subjects the CO_2 sensitivities determined from the rebreathing experiments were greater than those determined from the steady-state experiments. The average ratio S_r/S_s of 1·85 found in our study is in fair agreement with the results of Honda & Miyamura (1972) and Jacobi *et al.* (1987). Since the results of this study are manifestly different from Read's (1967) findings our results need a detailed discussion. The variability of the results of the rebreathing experiments between runs in the same subject are in good agreement with the variability found in the experiments of Read (1967) and Sahn, Zwillich, Dick, McCullough, Lakshiminarayan & Weil (1977), who reported coefficients of variation of 16 and 17·9 %, respectively.

Imposing a ventilation greater than 50 l min^{-1} in a steady-state experiment is uncomfortable for the subject, and this discomfort may influence the ventilatory response. To avoid this we limited the steps in P_{ET,CO_2} so that the ventilation did not exceed 50 l min^{-1}. In order to compare the same ventilation range in the rebreathing experiments only data of the first 3 min were analysed. This is in contrast to Read (1967), who used 4 min of rebreathing to obtain S_r. In order to establish whether there is a difference in slopes between data from 3 and 4 min of rebreathing, we compared the slopes obtained after 3 and 4 min of rebreathing in twenty-five experiments. There was no statistically significant difference ($P = 0·5$, analysis of variance). Although the mean peak ventilation was 10 l min^{-1} lower in the steady-state experiments, it has been shown that the steady-state response remains linear up to 50 l min^{-1} (Read, 1967) and 80 l min^{-1} (Linton *et al.* 1973).

The step increase in P_{ET,CO_2} (A) and the rate of rise of P_{ET,CO_2} (R) was assessed in all rebreathing experiments (see Table 1). The mean values of A and R were 1·5 kPa and 0·53 kPa min^{-1} respectively. The average ratio A/R was 3·0. Read reported a rate of rise of P_{ET,CO_2} ranging from 0·5 to 0·8 kPa min^{-1}. He did not explicitly mention the step increase in P_{ET,CO_2}, but from his data a value of 1·3 kPa can be estimated. Our rate of rise shows the same variability as that in Read's experiments,

but our mean value lies towards his lower limit. The rate of rise of P_{ET,CO_2} is influenced by the CO_2 stores in the body (Fowle & Campbell, 1964), oxygen consumption, the dead space of the experimental set-up and the volume of the lung at the moment of connection to the rebreathing bag. Since in our experiments the experimental dead space was only 280 ml, it is unlikely that this can explain the difference in rates of rise found by Read and ourselves. The other factors mentioned may have contributed to the smaller rate of rise in our group of subjects. The ratio A/R is approximately 2·2 min in Read's experiments. Berkenbosch, DeGoede, Olievier & Schuitmaker (1986) studied in anaesthetized cats the relationship of the relative slope of the CO_2 response curve following a step-ramp input and the ratio A/R. They defined relative slope as the difference in slope between the non-steady state and the steady state as a fraction of the steady-state slope. Their results show that this function is linear with a slope of 0·15 min^{-1}. A change in A/R of 1 min yields a change in non-steady-state slope of 15%. Assuming this relationship obtained from cats also applies to man, a reduction of 1 min in A/R would result in a ratio S_r/S_s of the order of 1·6 in our experiments.

We used a different technique from that of Read to obtain steady-state conditions. We obtained our steady-state data points by keeping end-tidal P_{CO_2} constant for 8 min. We observed that ventilation attained a steady state after approximately 5 min. This is in agreement with the findings of others (for instance see Ward & Bellville, 1983). Read (1967) obtained his data points by having subjects inhale various gas mixtures with constant CO_2 concentrations for 20 or 30 min, the time necessary to obtain the steady state, whilst the *inspired* CO_2 concentration was kept constant.

From the above discussion it is clear that the small differences in protocol cannot explain the striking difference between our findings and those of Read (1967).

Honda & Miyamura (1972) interpreted the difference they found in steady-state slopes and rebreathing slopes as an altered neurogenic activity in the ventilatory control system, suggesting that the increased ventilatory response is a time-dependent phenomenon, which only exists until the steady state is reached. Such an interpretation can serve as an example for the general feeling that the slope obtained from Read's method should be the same as the slope obtained from the steady-state method, and that any difference must be explained by mechanisms other than those considered by Read & Leigh (1967).

The reason for not detecting a difference in response slopes in Read's (1967) experiments was attributed by Read & Leigh (1967) to the relatively small P_{ET,CO_2} range covered in the steady-state experiments and the variability of repeated experiments. They also suggested an effect of the peripheral chemoreceptors resulting in a minimized theoretical difference in slopes of the ventilatory response curves to CO_2 as defined by rebreathing and steady-state methods. In our experiments the same relative P_{ET,CO_2} range is covered in the steady-state experiments and our variability of responses is of the same order of magnitude as in Read's (1967) experiments. Since there is general agreement that during hyperoxia the peripheral chemoreceptors are silent (Cunningham, Robbins & Wolff, 1986), it is clear that they cannot influence the slope of the rebreathing curves. We suggest that a more important reason for not detecting a difference in slopes is the small number

of subjects and experiments on which the comparison of both methods was based. This is also true for the experiments of Clark (1968) and Linton *et al.* (1973).

Lambertsen *et al.* (1963) and Nishimura *et al.* (1987) determined the $\dot{V}_E$–internal jugular venous P_{CO_2} (P_{jv,CO_2}) response during hyperoxia, simultaneously with the $\dot{V}_E$ –P_{a,CO_2} response. Both groups of investigators found a steeper slope for the $\dot{V}_E$–P_{jv,CO_2} curve compared to the $\dot{V}_E$–P_{a,CO_2} curve. The ratio of these slopes was 1·5 in the experiments of Lambertsen *et al.* (1963) and 1·4 in the experiments of Nishimura *et al.* (1987). This can be explained by the increase in cerebral blood flow during hypercapnia, which in the steady state leads to a smaller arterial–jugular venous P_{CO_2} gradient. Kety & Schmidt (1948) and Fencl *et al.* (1969) demonstrated in healthy subjects that during CO_2 inhalation the increase in the jugular venous P_{CO_2} is about one-half of that in arterial blood. Assuming that P_{jv,CO_2} only slightly differs from P_{t,CO_2}, one would expect the slope of the rebreathing response to be 40–100 % larger than the steady-state slope.

If we assume that P_{t,CO_2} is equal to cerebral venous P_{CO_2} (P_{cv,CO_2}), and that ventilation is instantaneously and linearly related to P_{t,CO_2} with slope S_t, the measured slope S_r equals the slope S_t. Our analysis (see Appendix) suggests that the ratio S_t/S_s can easily range from 4/3 to 2 depending on the values of parameter γ, which 'locates' P_{t,CO_2} between P_{a,CO_2} and P_{cv,CO_2} in the steady state, and parameter β, which equals the ratio $\Delta P_{cv,CO_2}/\Delta P_{a,CO_2}$ between steady states. A ratio $S_t/S_s = 4/3$ is obtained by taking $\beta = 0{\cdot}5$ and $\gamma = 0{\cdot}5$ ($P_{t,CO_2} = (P_{cv,CO_2} + P_{a,CO_2})/2$; cf. Pontèn & Siesjö, 1966, in cats). A ratio $S_t/S_s = 2$ is obtained by assuming $\gamma = 0$ ($P_{cv,CO_2} = P_{t,CO_2}$) and $\beta = 0{\cdot}5$ (Kety & Schmidt, 1948; Fencl *et al.* 1969). The ratio S_r/S_s found by us also suggests that P_{t,CO_2} is close to P_{cv,CO_2} and that the ratio $\Delta P_{cv,CO_2}/\Delta P_{a,CO_2}$ is of the order of 0·5 between steady states.

The difference in slopes obtained from the steady state and Read's rebreathing method presented in this study can therefore readily be explained by Read & Leigh's (1967) theoretical model, as discussed in the Appendix. This difference is the result of the increase in cerebral blood flow caused by the increase in carbon dioxide tension. In the simulations of Read & Leigh (1967) the change in cerebral blood flow with P_{t,CO_2} was too low, so that the steady-state CO_2 sensitivity was overestimated.

As shown in the Appendix the step A and rate of rise R needed to realize Read's conditions equal about 1·2 kPa and 0·8 kPa min^{-1}, respectively. These values are closer to the magnitude of A and R found in Read's (1967) experiments than to the ones found in our experiments. However, it should be kept in mind that the values of the parameters used to calculate A and R are not precisely known so that slight deviations for both A and R are acceptable.

As our results suggest that P_{t,CO_2} is close to P_{cv,CO_2} one may speculate that the slope of the ventilatory response obtained with Read's rebreathing method does not represent the steady-state CO_2 sensitivity but rather the slope of the ventilatory response as a function of P_{t,CO_2}, viz. S_t. This was already implied by Read & Leigh (1967) but its significance was not appreciated due to Read's (1967) experimental findings.

To gain more insight into the effect of a step-ramp input in P_{ET,CO_2} on the ventilatory response a large range of steps, A, and rates of rise, R, have to be applied. This will not only show the effect of the variation of A and R but will also indicate

whether steps and rates of rise can be found to acquire the steady-state response slope.

APPENDIX

Closely following Read & Leigh (1967) we write the mass balance for CO_2 for a brain compartment as

$$\frac{dP_{t,CO_2}}{dt} = \frac{l_a}{l_t}\dot{Q}(P_{a,CO_2} - P_{cv,CO_2}) + \frac{\dot{M}}{l_t} - \frac{(b_v - b_a)\dot{Q}}{l_t}, \tag{1}$$

where P_{t,CO_2} is the brain tissue P_{CO_2}, P_{a,CO_2} the arterial P_{CO_2} and P_{cv,CO_2} the cerebral venous P_{CO_2}. $\dot{Q}$ and $\dot{M}$ are the brain blood flow density and brain metabolism density, respectively. In deriving eqn (1) we have used linear approximations to the blood and brain tissue CO_2 dissociation curve, viz. l_t is the slope of the brain tissue, l_a the slope of the blood CO_2 dissociation curve, and b_a and b_v the intercepts of the arterial and venous CO_2 dissociation curves. As $(b_v - b_a)$ is approximately inversely proportional to $\dot{Q}$, we introduce the Haldane parameter $h = (b_v - b_a)\dot{Q}$ (Read & Leigh, 1967) and arrive at:

$$\frac{dP_{t,CO_2}}{dt} = \frac{l_a}{l_t}\dot{Q}(P_{a,CO_2} - P_{cv,CO_2}) + \frac{\dot{M} - h}{l_t}. \tag{2}$$

We further assume that (cf. Adams, Glasheen & Severns, 1984)

$$P_{t,CO_2} = P_{cv,CO_2} - \frac{\gamma(\dot{M} - h)}{l_a \dot{Q}}, \tag{3}$$

in which γ is a parameter which 'locates' P_{t,CO_2} between P_{a,CO_2} and P_{cv,CO_2} $(0 < \gamma < 1)$ in the steady state. Substituting eqn (3) in eqn (2) we find

$$\frac{dP_{t,CO_2}}{dt} = \frac{l_a}{l_t}\dot{Q}(P_{a,CO_2} - P_{t,CO_2}) + \frac{(1-\gamma)}{l_t}(\dot{M} - h). \tag{4}$$

Finally we assume that the ventilation ($\dot{V}_E$) is instantaneously and linearly related to P_{t,CO_2} so that we may write

$$\dot{V}_E = S_t P_{t,CO_2} + k_t, \tag{5}$$

in which S_t is the CO_2 sensitivity measured 'at the site' of the central chemoreceptors and k_t is a constant. The Read rebreathing method is characterized by a step increase A from P_{a,CO_2} to P_{t,CO_2}, equal to

$$A = \frac{(1-\gamma)}{l_a \dot{Q}_0}(\dot{M} - h), \tag{6}$$

and a linear rate of rise R of P_{a,CO_2}. In eqn (6) $\dot{Q}_0$ is the blood flow just before the applied step A. As P_{t,CO_2} is also required to rise linearly we find

$$P_{t,CO_2} = P^0_{t,CO_2} + Rt, \tag{7}$$

with

$$R = \frac{(1-\gamma)}{l_t}(\dot{M} - h). \tag{8}$$

In other words, applying a step in P_{a,CO_2}, which reduces the tissue–arterial CO_2 difference to zero and a rate of rise given by eqn (8), we see that P_{t,CO_2} increases with the same rate of rise. Equations (6) and (8) may be called the Read conditions. Using $l_t = 2{\cdot}25 \times 10^{-2}$ ml ml^{-1} kPa^{-1}, $l_a = 3{\cdot}22 \times 10^{-2}$ ml ml^{-1} kPa^{-1}, $\gamma = 0$, $\dot{M} = 5 \times 10^{-4}$ ml ml^{-1} s^{-1}, $\dot{Q}_0 = 8{\cdot}3 \times 10^{-3}$ ml ml^{-1} s^{-1} and $h = 1{\cdot}83 \times 10^{-4}$ ml ml^{-1} s^{-1}, A and R are 1·2 kPa and 0·8 kPa min^{-1}, respectively. Note that there is only one step-ramp input function which satisfies the Read condition (cf. Berkenbosch *et al.* 1986). Due to eqn (5) $\dot{V}_E$ also changes linearly with time and the ventilatory slope of $\dot{V}_E$ *vs.* P_{a,CO_2} is S_t.

In steady states we assume for small changes that to a first approximation

$$\Delta P_{cv,CO_2} = \beta \Delta P_{a,CO_2}. \tag{9}$$

From eqns (2) and (4) in the steady state and eqn (9) it can readily be derived that

$$\frac{S_t}{S_s} = \frac{1}{\beta + \gamma - \beta\gamma}, \tag{10}$$

in which S_s is the CO_2 sensitivity in the steady state. Taking $\gamma = 0$ ($P_{t,CO_2} = P_{cv,CO_2}$) and $\beta = 0{\cdot}5$ (Kety & Schmidt, 1948; Fencl *et al.* 1969) we find $S_t/S_s = 2$. Substituting $\gamma = 0{\cdot}5$ (Pontèn & Siesjö, 1966) and $\beta = 0{\cdot}5$ we have $S_t/S_s = \frac{4}{3}$. From their theoretical analysis, Read & Leigh (1967) found a difference between the slopes of the rebreathing and steady-state methods of roughly 30%. Therefore it is to be expected that a difference in the slopes obtained from the steady-state and the Read rebreathing method can readily be detected from the background of the experimental scatter.

REFERENCES

Adams, J. M., Glasheen, W. P. & Severns, M. L. (1984). Estimating medullary chemoreceptor blood flow from ventilatory-CO_2 response transients: Theory and data from anesthetized dogs. *Annals of Biomedical Engineering* **12**, 1–13.

Berkenbosch, A., DeGoede, J., Olievier, C. N. & Schuitmaker, J. (1986). A pseudo-rebreathing technique for assessing the ventilatory response to carbon dioxide in cats. *Journal of Physiology* **381**, 483–495.

Clark, T. J. H. (1968). The ventilatory response to CO_2 in chronic airways obstruction measured by a rebreathing method. *Clinical Science* **34**, 559–568.

Cunningham, D. J. C., Robbins, P. A. & Wolff, C. B. (1986). Integration of respiratory responses to changes in alveolar partial pressures of CO_2 and O_2 and in arterial pH. In *Handbook of Physiology*, section 3, *The Respiratory System*, vol. 2, *Control of Breathing*, part 2, ed. Fishman, A. P., Cherniack, N. S., Widdicombe, J. G. & Geiger, S. R., pp. 475–528. Bethesda, MD, USA: American Physiological Society.

Drummond, G. B. & Goodenough, P. C. (1977). Automatic correction for drift in an integrator for phasic signals. *Medical and Biological Engineering and Computation* **15**, 688–691.

Fencl, V., Vale, J. R. & Broch, J. A. (1969). Respiration and cerebral blood flow in metabolic acidosis and alkalosis in humans. *Journal of Applied Physiology* **27**, 67–76.

Fowle, A. S. E. & Campbell, E. J. M. (1964). The immediate carbon dioxide storage capacity of man. *Clinical Science* **27**, 41–49.

Honda, Y. & Miyamura, M. (1972). Increased ventilatory response to CO_2 by rebreathing in consecutive daily trials. *Japanese Journal of Physiology* **22**, 13–23.

Jacobi, M. S., Patil, C. P. & Saunders, K. B. (1987). Comparison of transient, steady state and rebreathing methods measuring the ventilatory response to carbon dioxide in man. *Journal of Physiology* **394**, 58*P*.

KETY, S. S. & SCHMIDT, C. F. (1948). The effects of altered arterial tension of carbon dioxide and oxygen in cerebral blood flow and cerebral oxygen consumption of normal men. *Journal of Clinical Investigation* **27**, 484–492.

LAMBERTSEN, C. J., HALL, P., WOLLMAN, H. & GOODMAN, M. W. (1963). Quantitative interactions of increased P_{O_2} and P_{CO_2} upon respiration in man. *Annals of the New York Academy of Sciences of the USA* **109**, 731–742.

LANDMESSER, C. M., COBB, S., PECK, A. S. & CONVERSE, J. G. (1957). Respiratory responses to carbon dioxide 'transients' in normal volunteers. *Anesthesiology* **18**, 807–830.

LINTON, R. A. F., POOLE-WILSON, P. A., DAVIES, R. J. & CAMERON, I. R. (1973). A comparison of the ventilatory response to carbon dioxide by steady-state and rebreathing methods during metabolic acidosis and alkalosis. *Clinical Sciences and Molecular Medicine* **45**, 239–249.

NISHIMURA, M., SUZUKI, A., NISHIURA, Y., YAMAMOTO, H., MIYAMOTO, K., KISHI, F. & KWAKAMI, Y. (1987). Effect of brain blood flow on hypoxic ventilatory response in humans. *Journal of Applied Physiology* **63**, 1100–1106.

PONTÈN, U. & SIESJÖ, B. K. (1966). Gradients of CO_2 in the brain. *Acta physiologica scandinavica* **67**, 129–140.

READ, D. J. C. (1967). A clinical method for assessing the ventilatory response to carbon dioxide. *Australasian Annals of Medicine* **16**, 20–32.

READ, D. J. C. & LEIGH, J. (1967). Blood–brain tissue P_{CO_2} relationships and ventilation during rebreathing. *Journal of Applied Physiology* **23**, 53–70.

REBUCK, A. S. & SLUTSKY, A. S. (1981). Measurement of ventilatory responses to hypercapnia and hypoxia. In *Regulation of Breathing*, part II, ed. HORNBEIN, T. F., pp. 745–772. New York: Marcel Dekker, Inc.

SAHN, S. A., ZWILLICH, C. W., DICK, N., MCCULLOUGH, R. E., LAKSHIMINARAYAN, S. & WEIL, J. V. (1977). Variability of ventilatory responses to hypoxia and hypercapnia. *Journal of Applied Physiology* **43**, 1019–1025.

WARD, D. S. & BELLVILLE, J. W. (1983). Effect of intravenous dopamine on hypercapnic ventilatory response in humans. *Journal of Applied Physiology* **55**, 1418–1425.